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EC EMERGENCY MEDICINE AND CRITICAL CARE
Research Article

The Incidence of Chronic Thromboembolic Pulmonary Hypertension based on Echocardiography Finding After Acute Pulmonary Embolism in Omani Population

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Received: April 24, 2021; **Published:** May 17, 2021

Abstract

Background: Chronic thromboembolic pulmonary hypertension (CTEPH) is a common and fatal sequel of acute pulmonary embolism (APE) however it is potentially curable without the need for lung transplantation. The estimated incidence of CTEPH is about 0.5 to 3.8% in a patient after an acute single episode of pulmonary embolism. It is important to detect CTEPH and to prevent its progression. We aimed to determine the incidence of CTEPH based on Echocardiography findings and identify its associated risk factors in Omani adult population after acute pulmonary embolism (APE).

Methods: Out of 372 patients who have confirmed APE, 57 patients were enrolled in the study as they met the inclusion criteria and have echocardiography done at least 3 months from the diagnosis of APE. Risk factors were classified according to CT extension of the APE and etiology of the PE in the studied population.

Results: 57 patients were included in this study with a mean age of 48 years and almost equal percentage of patients were observed in each gender. 39 patients (68.4%) had bilateral APE with 47 patients (82.5%) and 10 patients (17.5%) presented with proximal and distal APE, respectively. The number/percentage of patients with risk factors for thromboembolism, lupus anticoagulant, unclassified thrombophilia, factor V Leiden deficiency, idiopathic, and malignancy, were 14 (24.6%), 1 (1.8%), 3 (5.3%), 3 (5.3%), and 9 (15.8%), respectively, while the percentage/number of patients with unknown risk factors were 2 (3.5%), and provoked APE were 25 (43.9%). The pulmonary arterial systolic pressure was found to be high, > 35 mmHg, in 13 patients (22.8%). Right ventricular and right atrial dilatations were observed in 6 patients (10.5%). Four patients (7%) have CTEPH confirmed with right heart catheterization and are already in follow up with chest medicine department. The association between risk factors and outcomes was declined because of the small sample size.

Conclusion: The incidence of CTEPH based on echo is high as 22.8% based on high PASP and 10.5% based on right sided heart dilatation/dysfunction, while only four patients (7%) of them has confirmed CTEPH after right heart catheterization. A lot of them has lost follow up because there were no previous guidelines to follow up for CTEPH.

***Keywords**: Acute Pulmonary Embolism; CTEPH; Echocardiography; High Pulmonary Pressure*

Introduction

Chronic thromboembolic pulmonary hypertension (CTEPH) is a potentially curable condition without the need for lung transplantation [6]. It is considered in pulmonary hypertension as group IV when pulmonary arterial pressure is found to be more than 20 mmHg, features of organized chronic thrombus in pulmonary arteries and/or presence of perfusion defect [1,8].

Patients who have acute pulmonary embolism may develop right ventricular strain that resolves in the majority of patients after a few weeks of initiation of the anticoagulation or other treatment modalities. However, in patients with CTEPH, this does not resolve despite

treatment [2]. The pathophysiology of CTEPH can be explained by the unresolved or persistent thrombus formation with consequent fibrous stenosis and or obliteration of pulmonary arteries, resulting in persistent pulmonary perfusion defect. Hence, this leads to an increase in pulmonary arterial resistance with an increase in pulmonary pressure [2-4].

There are risk factors for CTEPH which are divided into chronic medical conditions, thrombotic factors and genetic factors. The other risk factors are specific to the pulmonary embolism at diagnosis which are recurrent PE, unprovoked PE, large perfusion defect, young or old age, high pulmonary arterial systolic pressure > 50 mmHg, persistent pulmonary hypertension at 6 months after acute PE. Cancer, Thyroid replacement therapy, chronic inflammatory disorders, post-splenectomy and infected surgical cardiac shunts or pacemaker or defibrillator leads were examples of chronic medical conditions. The thrombotic factors are lupus anticoagulant, antiphospholipid antibodies, high levels of factor VIII and dysfibrinogenemia. The genetic factors are ABO blood, HLA polymorphism, and abnormal endogenous fibrinolysis [8,9].

Diagnosis of CTEPH can be considered initially by echocardiography and VQ scan, where the pulmonary arterial systolic pressure is high > 35 mmHg, and perfusion defect is identified, respectively. Once the diagnosis is expected, it should be confirmed by right heart catheterization with invasive measurement of mean pulmonary arterial pressure (mPAP) and pulmonary vascular resistance (PVR). The other diagnostic modalities may be required for surgical mapping are CT pulmonary angiography and conventional pulmonary angiography to determine the site of the chronic thromboembolism and so the type of treatment that needs to be considered [6].

When this condition is diagnosed in a patient, he/she should be evaluated by a multidisciplinary team to decide regarding the possibility of surgical endarterectomy. Otherwise, the patient may be offered medical therapy of pulmonary arterial hypertension. The surgery may result in a significant improvement and or normalization of right heart hemodynamic and function [6].

The prevalence of CTEPH is estimated to be 0.1 to 0.5% in those who survived APE [7]. The estimated incidence of CTEPH is about 0.5 to 3.8% in patient with an acute single episode of pulmonary embolism [5]. There is no clear recommendation for the proper follow up after APE to look for this condition because of low prevalence and incidence. Furthermore, there is no national study to look at the prevalence of CTEPH in Oman.

Aim of the Study

This study was conducted to look for the incidence of CTEPH based on Echocardiography and identify the associated risk factors in the Omani adult population after APE. The other aim of this study is to suggest recommendations for proper follow up for the patients with APE for early diagnosis of CTEPH.

Methods

This is a retrospective analysis study of prospectively collected data, which was conducted at the Royal Hospital (RH), Muscat, Oman. The RH is the tertiary hospital that provide complex management of all cardio-thoracic medical and surgical disorders for the whole country and all cases referred to it. The study was approved by the local ethics committee at the RH. The RH has an excellent medical record system, where data is computerized and had received a well-recognized international certificate of excellence for the electronic medical system called "Al Shifaa". All data including clinical, laboratory and radiological data were collected prospectively from Al-Shifaa system.

All patients who were diagnosed as APE, from January 2006 to December 2015, were studied, which were about 372. About 15 patients, non-Omani patients and pediatric group (< 18 years of age) were excluded from the study. Those included patients are required to have their diagnoses of APE to be confirmed with contrast-enhanced CT, or a high probability index in ventilation perfusion scan. The distribution of APE was classified based on site as segmental/subsegmental and unilateral/bilateral. Patients with radiological features

of chronic pulmonary thrombo-embolism were excluded. All patients had an echocardiography done at least three months after the diagnosis of APE. Patients who did not have a follow up echocardiography at > 3 months, missed their follow up, or did not meet the inclusion criteria were excluded. The included population were 57 patients whom met inclusion criteria and about 315 patients were excluded for above mentioned reasons.

Patients who had other co-morbid conditions that could raise the pulmonary pressures and impair right heart function were also excluded (e.g. Chronic moderate to severe lung disease, connective tissue diseases-related pulmonary hypertension, structural heart disease, and poor left ventricular function with low ejection fraction, < 35%).

The data collected for each patient included demographic information (e.g. age at diagnosis of APE, and gender), the possible risk factors for CTEPH (e.g. etiological cause of APE) and the site/distribution of APE.

The echocardiography on follow up (at 3 months or more after APE and treatment initiation) was reviewed during data collection and the following parameters were recorded: systolic pulmonary arterial systolic pressure (more than 35 mmHg) and the right ventricular/atrial dilatation. Finally, the cases whom found to fit the CTEPH criteria based on Echo (high mean pulmonary pressure or right ventricular abnormalities) were studied if they have already follow up with chest medicine and if on treatment.

The demographic information, etiological factors of APE, radiological findings of APE, echocardiographic findings and final confirmation of CTEPH (by both V/Q scan and right heart catheterization) were initially collected in data collection sheets. The information was entered in Excel sheets and then converted to SPSS for final data analysis. Descriptive statistics (median and standard deviation) were used to describe the quantitative and categorical study variables. With the help of statistician, the percentage of patients, age was stratified according to mean and median. Other information was analyzed with the percentages. The association between risk factors (CT findings, etiological factors, high PASP, and RV/RA dilation) were analyzed using chi-square testing. The significance of association of risk factors and outcome were not analyzed because of small sample size.

Results

Figure 1 shows the flow chart of the participants. Out of 372 patient records, only 57 patients were identified to meet the inclusion criteria. Other patients were excluded because they were non-Omani, lost follow up, died at diagnosis, and/or had exclusion factors. The mean age of diagnosis was 48 ± 25 years, and 31 (54.4%) of the patients were female. Thirty-nine patients (68.4%) had bilateral APE with 47 (82.5%) had predominantly a proximal disease. The number of patients with known risk factors, lupus anticoagulant, thrombophilia (unspecified), factor V Leiden deficiency, idiopathic, unknown, malignancy and provoked APE, were 14 (24.6%), 1 (1.8%), 3 (5.3%), 3 (5.3%), 2 (3.5%), 9 (15.8%), and 25 (43.9%), respectively. Out of 57 patients, 3 (5.3%) received thrombolysis.

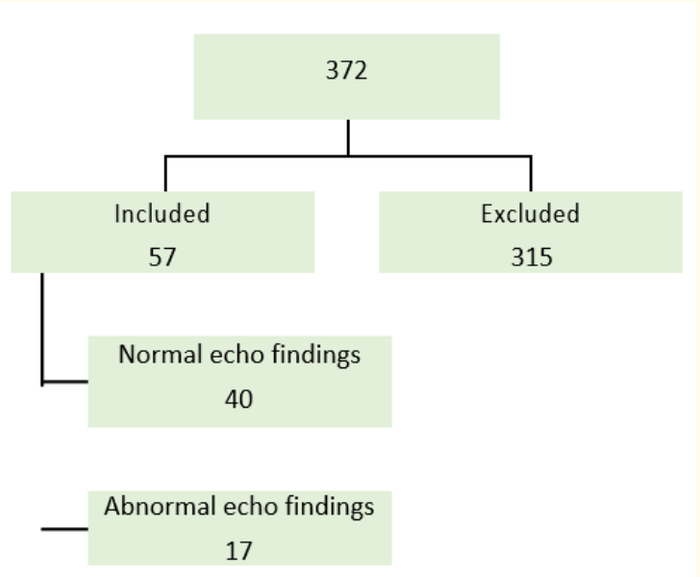

Figure 1: *Shows the flow chart of the participants, out of 372 patients, only 57 patients were identified to meet the inclusion criteria and 17 had abnormal echocardiographic findings.*

The estimated pulmonary arterial systolic pressure was found to be high, > 35 mmHg, in 13 patients (22.8%) by echocardiography done > 3 months after the diagnosis of APE. Right ventricular and right atrial dilatations were observed in 6 patients (10.5%). Four patients (7%) has CTEPH confirmed (by both V/Q scan and right heart catheterization) and in follow up with chest medicine department.

Table 1 illustrates the number and percentage of PASP (high and normal) and RV/RA (dilatation and normal), by gender, CT distribution, site in CT scan and the risk factors.

		PASP		RV/RA	
		High	Normal	Dilatation	Normal
Gender	Male (n = 26)	4 (15.4%)	22 (84.6%)	4 (15.4%)	22 (84%)
	Female (n = 31)	9 (29%)	22 (71%)	2 (6.5%)	29 (93.5%)
CT Distribution	Bilateral (n = 39)	10 (25.6%)	29 (74.4%)	4 (10.3%)	35 (89.7%)
	Unilateral (n = 18)	3 (16.7%)	15 (83.3%)	2 (11.1%)	16 (88.9%)
Site in CT	Proximal (n = 37)	12 (25.5%)	35 (79.5%)	4 (8.5%)	43 (91.5%)
	Distal (n = 10)	1 (10%)	9 (20.5%)	2 (20%)	8 (80%)
	Lupus AC (n = 14)	2 (14.3%)	12 (85.7%)	1 (7.1%)	13 (92.9%)
	Thrombophilia (not specified) (n = 1)	1 (100%)	0 (0%)	0 (0%)	1 (100%)
	Factor V Leiden Deficiency (n = 3)	0 (0%)	3 (100%)	0 (0%)	3 (100%)
Risk Factors	Idiopathic (n = 3)	2 (66.7%)	1 (33.3%)	1 (33.3%)	2 (66.7%)
	Unknown (n = 2)	1 (50%)	1 (50%)	0(0%)	2 (100%)
	Malignancy (n = 9)	3 (33.3%)	6 (66.7%)	1 (11.1%)	8 (88.9%)
	Provoked (n = 25)	4 (16%)	21 (84%)	3 (12%)	22 (88%)

Table 1: *Shows the number and percentage of PASP (high and normal) and RV/RA (dilatation and normal), by gender, CT distribution, site in CT scan and the risk factors.*

Discussion and Conclusion

To the best of our knowledge, this is the first paper from the region that examined the incidence of chronic thromboembolic pulmonary hypertension based on echocardiography after APE. The participants were young and with a slight female predominance. About two thirds of the patients had bilateral APE with the majority having a proximal disease. The main risk factors were lupus anticoagulant and provoked APE.

In this study, the incidence of chronic thromboembolic pulmonary hypertension based on echocardiography after acute pulmonary embolism was as high as 22.8% based on high PASP and 10.5% based on right-sided heart dilatation/dysfunction. As compared to a Korean study looking for the predictive value of echocardiography for CTEPH after APE that found the incidence to be as high as 66.7% based on RV dilatation [10]. Other well-designed studies following standardized diagnostic algorithms found the incidence of CTEPH to range from 0.5 to 3.8% [7]. This clearly illustrates that echocardiographic may overestimate the true incidence of CTEPH and further diagnostic methods that include both imaging and hemodynamics are needed for such estimation.

As noted, most risk factors recorded was lupus anticoagulant. This can be explained by the fact that those patients are under regular follow up with rheumatology, where echocardiography is a part of the screening surveillance of SLE. Other patients did not have the same privilege as the awareness about CTEPH is low and, until recently, there was no specific recommendation about post APE screening. The screening for CTEPH after APE based on symptoms and functional status were only recently recommended by the European Respiratory Society, when the guidelines advised to assess for dyspnea and/or the functional limitation at 3 to 6 months after the diagnosis of APE, and if any, transthoracic echocardiography needs to be done as the first screening tool of CTEPH [8,9].

Deficiencies in our system were detected and contribute to the difficulties in picking up all patients at risk. First, there was no specific protocol to follow up patients after APE. As such, only a small number of the population collected had an appropriate follow up with chest medicine and clinical hematology in regard to continuation/cessation of treatment. However, the rest were referred to local health centers to be followed by a general practitioner for 3 - 6 months of anticoagulation and no specific recommendation for screening or proper evaluation. Second, some of the patients who presented with inherited diseases for increasing coagulopathy with provoked risk factors for APE were not referred or evaluated by clinical hematology confirming the weakness in our system in regard to this disease. Third, missing information was one of the great challenges to the study.

This study has a few limitations. First, the included patients were the ones who had echocardiography done after the APE for other medical conditions. In contrast the majority of the patients lost to follow up for different reasons. Therefore, the sample size was small. Second, the association of the risk factors with the clinical outcome was not possible because of the small sample size. Third, being a retrospective observational study, it is subjective to well-known weaknesses and limitations, and the confounding variables were not adequately evaluated and controlled for. Forth, the echocardiography report, which is technician dependent, has its own limitation as a diagnostic tool in pulmonary hypertension, and the lack of right heart catheterization measurements is the major limitation in our study.

The future recommendation for similar study is to follow up all APE patients prospectively for at least 3 - 6 months. Those who have persistent symptoms or functional limitation should be evaluated by echocardiography and followed up in clinical hematology and chest medicine.

In conclusion, the incidence of CTEPH based on echocardiography is high, but that does not make a definitive diagnosis of this condition. It is important to follow up all patients with APE to ensure complete resolution of the thromboembolic disease and to stratify patients at risk of developing CTEPH.

Key Messages

1. Incidence of CTEPH are APE based on echocardiography is as high as 22.8% based on high sPAP and 10.5% based on right-sided heart dilatation/dysfunction, which requires further confirmation by imaging modalities, namely V/Q scanning, and right heart catheterization.

2. There should be a set of recommendation for follow up for patients with APE.

Bibliography

1. Nicholas A Boon., *et al*. "Davidson Principles and Practice of Medicine". 20th Edition, Elsevier (2006): 39.

2. Guerin L., *et al*. "Prevalence of Chronic Thromboembolic Pulmonary Hypertension are Acute Pulmonary Embolism". *Thrombosis and Haemostasis* 112.3 (2014): 598-605.

3. G Wirth., *et al*. "Chronic Thromboembolic Pulmonary Hypertension (CTEPH) – Potential Role of MulW detector-Row CT (MD-CT) and MR Imaging in the Diagnosis and Differential Diagnosis of the Disease". *Rofo* 186.8 (2014): 751-761.

4. Keith McNeil and John Dunning. "Chronic thromboembolic pulmonary hypertension (CTEPH)". *Heart* 93.9 (2007): 1152-1158.

5. I Kayaalp., *et al*. "The incidence of chronic thromboembolic pulmonary hypertension secondary to acute pulmonary thromboembolism". *Tüberküloz ve Toraks* 62.3 (2014): 199-206.

6. Nick H Kim., *et al*. "Chronic Thromboembolic Pulmonary Hypertension". *Journal of American College of Cardiology* 62.25 (2013): D92-D99.

7. ChrisWan Gerges., *et al*. "Right ventricle in acute and chronic pulmonary embolism (2013 Grover Conference series)". *Pulmonary Circulation* 4.3 (2014): 378-386.

8. Piazza G and Goldhaber S. "Chronic Thromboembolic Pulmonary Hypertension". *The New England Journal of Medicine* 364 (2011): 351-360.

9. V Konstan Wnides., *et al*. "2019 ESC Guidelines for the diagnosis and management of acute pulmonary embolism developed in collaboration with the European Respiratory Society (ERS)". *European Respiratory Journal* 54.3 (2019): 1901647.

10. Jin Sup Park., *et al*. "The predictive value of echocardiography for chronic thromboembolic pulmonary hypertension are acute pulmonary embolism in Korea". *Korean Journal of Internal Medicine* 32.1 (2017): 85-94.

Volume 5 Issue 6 June 2021